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# This Month in the *Journal*

This month in our series "Insights from Model Systems," we feature three reviews on the promise of genetic research in larger mammals. Ostrander and Giniger (p. 475) discuss the status of the Dog Genome Project and the advantages of working with the dog, a species with many distinct and homogeneous breeds. Palmour et al. (p. 481) discuss the potential of the vervet monkey as a system for studying complex behavioral phenotypes such as alcohol consumption. Rogers and Hixson describe work done with the baboon, a model for several complex multifactorial human diseases, such as atherosclerosis and osteoporosis.

***Private and Recurrent* TGM1 *Mutations,*** *by Laiho et al. (p. 529)*

Because of its long history of genetic isolation, the Finnish population is widely studied to follow the propagation of disease alleles, which typically arise from a small number of original founding events. However, Laiho and colleagues show here that autosomal recessive congenital ichthyosis (ARCI) in Finland is associated with numerous independent mutations. In ARCI, defects in the gene for transglutaminase 1 (*TGM1*) lead to insufficient cross-linking of proteins in the cornified cell envelope and to skin abnormalities including hyperkeratosis. Working with 38 affected families, Laiho et al. identify six distinct haplotypes, within which five distinct missense mutations are found in *TGM1*. A pair of adjacent arginine codons containing two neighboring CpG dinucleotides appears to be highly mutable, and transitions affecting one of these codons appear to have occurred many times independently, including at least three times among the Finns.

***Defects in the* Phosphorylase Kinase β *Gene,*** *by van den Berg et al. (p. 539)*

Phosphorylase kinase (PhK) is a key regulatory enzyme in the pathway that mobilizes glucose from stored glycogen, and defects in this multisubunit enzyme can affect several cell types, including hepatocytes, muscle, and erythrocytes. The β subunit of PhK is encoded by a single gene with at least two alternatively spliced exons expressed in distinct tissues. van den Berg et al. report here on a child with hepatomegaly and abnormal glycogen metabolism who is a compound heterozygote for point mutations in the gene for the β subunit. Although both mutations are apparent null alleles and affect exons common to all forms, PhK activity in her muscles and erythrocytes appears to be spared, and only her liver is affected. van den Berg et al. speculate that the αγδ form of the enzyme, which is unstable but active in vitro, may rescue PhK function in extrahepatic cells. The different requirement for the β subunit in the liver remains unexplained.

***Mutations in the* PKD2 *Gene,*** *by Veldhuisen et al. (p. 547)*

Veldhuisen and co-workers report a systematic analysis, by SSCP analysis, of mutations in the *PKD2* gene, one of three known genes related to the autosomal dominant form of polycystic kidney disease (PKD). In a group of 35 families in which PKD is linked to 4q, they find 16 mutations, of which all but 1 lead to premature termination codons and are expected to be null. Recently, it was shown that, in some people with PKD, cyst tissue has undergone loss of heterozygosity in the *PKD1* gene; loss of *PKD2* expression may lead to cyst development as well. The authors also note that, in 15 of the families, no mutation could be found. The additional mutations may be found in intronic or promoter regions or in the first exon, which was not amenable to SSCP analysis.

***Low-Penetrance Retinoblastoma,*** *by Bremner et al. (p. 556)*

*RB* is a tumor-suppressor gene whose expression is lost by loss of heterozygosity (LOH) in familial retinoblastoma and by loss of one or both alleles in other soft-tissue cancers and osteosarcomas. In most affected families, LOH leads to hemizygosity and disease in 95% of eyes, but Bremner et al. have examined a mutant *RB* allele found in a kindred with low penetrance of retinoblastoma. This in-frame deletion, which affects the domain of pRb that interacts with the growth-regulatory proteins MDM2 and E2F, may represent a weak allele in the retina, but it appears to be functionally null when expressed in an osteosarcoma cell line. As these authors suggest, this discrepancy raises the possibility of multiple roles for pRb in different cell types. It may also indicate a loss of normal growth-suppressor mechanisms in the osteosarcoma cell–culture model.

***Loricrin Mutation in Progressive Symmetric Erythrokeratoderma,*** *by Ishida-Yamamoto et al. (p. 581)*

Progressive symmetric erythrokeratoderma (PSEK) is a dominant skin disorder that presents with hyperkeratosis on the soles and palms and with erythema in irregular patches on the extremities. Ishida-Yamamoto and colleagues have now identified the molecular basis of this rare condition, which they studied in a family with three

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generations of affected individuals. Guided by the similarity, in histological appearance, between the keratotic plaques in PSEK and those seen in Vohlwinkel syndrome (VK), Ishida-Yamamoto et al. examined expression of loricrin, a cornified envelope component that is defective in VS. In erythematous tissue from this family, loricrin is depleted from the cornified envelope and accumulates in intranuclear granules. A frameshift mutation in the *loricrin* gene causes the C-terminal 91 amino acids of the protein to be replaced with a long stretch of missense sequence. Because the C-terminal domain contains many of the glutamine and lysine residues that participate in intermolecular cross-links, the dominant effect of this mutation probably arises from its ability to impair normal CE formation. These results show that PSEK is distinct from other erythrokeratodermas, in which the *loricrin* gene is not implicated, but show that PSEK and VS are allelic conditions.

***A Yeast Expression System for Human GALE,*** *by Quimby et al. (p. 590)*

Galactosemia, associated with mental retardation and hepatomegaly, can result from a lack of the enzyme UDP-galactose 4-epimerase (GALE), which interconverts the charged sugars UDP-galactose and UDP-glucose. Quimby et al. have examined the function of various *GALE* alleles expressed in yeast cells that were engineered to lack their endogenous epimerase gene. The two missense alleles identified in one compound-heterozygous child with epimerase-deficient galactosemia display distinct abnormalities in this expression system: One encodes a protein with reduced stability, and the other encodes a protein with altered biochemical properties. The coexpression of the two alleles in the same yeast strain leads to a dramatic loss of activity, consistent with allele-specific interactions between the expressed proteins.

***Uniparental Disomy of Chromosome 1,*** *by Pulkkinen et al. (p. 611)*

Adhesion of skin cells to the basement membrane at the dermal-epidermal boundary involves the binding of hemidesmosomes to extracellular-matrix components such as laminins; blistering diseases occur when any of these cell-surface or extracellular components are lacking. The lethal recessive disorder Herlitz junctional epidermolysis bullosa (H-JEB) results from a defect in genes for any of the subunits of laminin-5, a heterotrimeric protein that forms anchoring filaments in the lamina lucida. Pulkkinen and colleagues describe an unusual case of H-JEB in which the affected infant was homozygous for a nonsense mutation in the gene for the β3 subunit of laminin-5, because of maternal uniparental disomy (UPD). By following the maternal haplotypes associated with this disease allele, Pulkkinen et al. reconstruct the events in meiosis and zygotic development that may have led to UPD in this case.

***Chromosome 1p36 Deletion Syndrome,*** *by Shapira et al. (p. 642)*

With the advent of FISH it has become possible to identify subtle partial monosomies that might be missed or underdiagnosed otherwise. The recently identified deletion syndrome affecting the distal portion of 1p is one such condition, and the range of symptoms associated with it have not been well defined. Shapira and co-workers have now studied 13 children with distal 1p deletions who are free from any other known chromosomal abnormalities. The symptoms that they identify include skeletal, motor, and cognitive-developmental abnormalities and are quite variable within this group, and there is no evidence of a parent-of-origin effect. As with other contiguous gene–deletion syndromes, deletions are of variable length and may cause variable symptoms by haploinsufficiency at multiple sites or by uncovering recessive mutations.

***Multilocus Genotypes and Human Evolution,*** *by Mountain and Cavalli-Sforza (p. 705)*

Sequence variability at selectively neutral sites provides a reservoir of data from which the evolutionary history of human populations may be reconstructed. Polymorphic sites in the autosomes, the great majority of the genome, have not yet been widely exploited for this purpose. Now, Mountain and Cavalli-Sforza have analyzed RFLP data at a large number of such sites in 144 unrelated individuals from 12 populations. After calculating the number of shared polymorphisms between individuals, they derive a tree that depicts genetic distances. The consistency of this tree, the degree to which its clusters correspond to known ethnic affiliations or common geographic origins, reflects, in part, the number of generations that the populations have been isolated. The authors find that clustering of individuals on the tree is consistent within large geographic groupings (e.g., African vs. Asian) but not within ethnic groupings. The consistency observed can be used to estimate the period of separation between populations. Although the model does not explicitly address gene flow between groups, it allows the identification of individuals from recently immigrating families, who appear as outliers to the cluster of branches that represents their ethnic or geographical grouping.

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